

REMARKS

Upon entry of this Amendment B, claims 1-89, 91-119, 122-124, 127-131, 133, 137-141, 144, and 146-175 are pending and under consideration. Claim 132 was canceled by this amendment. All other claim cancellations were previously presented in Amendment A. Applicant expressly reserves the right to pursue these canceled claims in one or more continuation applications.

I. Obviousness-type Double Patenting Rejection

Reconsideration is respectfully requested of the rejection of claims 1-89, 91-119, 122-124, 127-133, 137-141 and 146-175 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-33 of US Pat. No. 6,638,973. Without conceding the propriety of the rejection, and in the interests of expediting prosecution, applicant submits herewith a terminal disclaimer in light of this reference.

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II. 35 USC §102 Rejections

Reconsideration is respectfully requested of the rejection of claims 1, 91-97, 109-112, 127-130, 137-138, and 165 under 35 USC §102(b) as being anticipated by the following references:

- 1) US 5,227,400;
- 2) US 5,250,683;
- 3) Georg et al., *Heteroaromatic Taxol Analogues: The Chemistry and Biological Activities of 3'-Furyl and 3'-Pyridyl Substituted Taxanes*, Bioorg. Med. Chem. Lett., 4(11), (1994);
- 4) Li et al., *Synthesis and Biological Evaluation of C-3'-Modified Analogs of 9(R)-dihydrotaxol*, J. Med. Chem., vol. 37, pp. 2655-2663 (1994);
- 5) US 5,489,601; and
- 6) WO 94/20485

The present claims are directed to taxanes having (1) a heterocyclo substituent at C3' (designated as "X₃"); (2) a hydroxy substituent at C7 (designated as "R₇"); and (3) an ester substituent at C10 (designated as "R₁₀"). With respect to the C10 ester, the claims require at least two carbon atoms in the ester group, in addition to the carbonyl carbon. Specifically, in claim 1, R₁₀ is defined as R_{10a}COO- where R_{10a} is hydrocarbyl, substituted hydrocarbyl or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contain carbon atoms in the alpha and beta positions relative to the carbon atom of which R_{10a} is a substituent. Thus, R_{10a} may **not** be a methyl group or a heterosubstituted methyl group, such groups only containing a

carbon atom in the alpha position with respect to the carbonyl carbon atom. This requirement, therefore, excludes the possibility of an acetoxy substituent (OAc) at C10.

The taxanes defined by claim 1 are novel in light of references **1 - 5** above because these references only disclose taxanes wherein the C10 substituent is acetoxy (OAc). Consequently, the disclosed taxanes fail to meet the requirements of claim 1.

In addition, the taxanes defined by claim 1 are novel in light of reference **6** because this reference only discloses exemplified taxanes having a hydroxy or oxo substituent at C10. In contrast, claim 1 requires a C10 ester moiety.

The taxanes defined by claim 91 are novel for the same reasons stated above. In addition to the requirements discussed above for the substituents at C3' and C10, claim 91 also requires that the taxanes have a C2 benzyloxy substituent, a C9 keto substituent and no substitution at C14 (i.e., R₁₄ is hydrido). Reference **6** discloses taxanes where the C9 substituent is other than keto. Thus, the taxanes of claim 91 are novel over reference **6** in at least two positions of the taxane.

Claims 92-97, 109-112, 127-130, 137-138, and 165 ultimately depend from either claim 1 or claim 91. Accordingly, these claims incorporate the requirements of the claims from which they depend. As such, these claims are also novel in light of references **1 - 6**.

III. 35 USC §103 Rejections

Reconsideration is respectfully requested of the rejection of claims 1-89, 91-119, 122-124, 127-133, 137-141, 144, 146-161, and 163-174 under 35 USC §103(a) as being unpatentable over references **1 - 6**.

As stated above, the present claims are directed to taxanes having (1) a heterocyclo substituent at C3'; (2) a hydroxy substituent at C7; and (3) an ester substituent at C10. Further, the ester group (R_{10a}) must contain at least two carbons adjacent to the carbonyl carbon, thereby eliminating acetoxy as an option. The cited references fail to suggest that taxanes having this combination of substituents would result in useful, active compounds.

All of the compounds recited in references **1 - 5** have a C10 acetoxy moiety. Importantly, the active taxane in the commercial product Taxol has a C10 acetoxy moiety. Thus, references **1 - 5** fail to even suggest that the C10 substituent should be modified in any way. If these references are combined with reference **6**, the modification at C10 results only in removal of the C10 acetoxy group in favor of a hydroxyl group (the moiety found in the commercial product Taxotere) or an oxo group. There is no suggestion that an ester group, other than acetoxy, would yield active taxanes.

In addition, the cited references do not disclose a method of preparing compounds having a C10 ester moiety, other than an acetoxymethyl group.

In contrast, the present claims require a taxane having an ester group, other than an acetoxymethyl, at the C10 position. Further, the data recited in the specification demonstrates that, in general, these taxanes have activity superior to that of Taxol and activity at least comparable to that of Taxotere (see Example 5). Specifically, 135 of the disclosed taxanes meet the current claim 1 requirements. Of those, 79% show activity better than Taxol and comparable to that of Taxotere. Unlike the cited references, the present application also provides a general scheme and an example for synthesizing the C10 ester substituted compounds of the present invention.

IV. 35 USC §112, Second Paragraph Rejection

Reconsideration is respectfully requested of the rejection of claim 165 under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, the Office asserts that the terms "esters", "ethers", "acetals", and "ketals" have no apparent bond to attach to the molecule and that the term "thiol" is ambiguous.

A person skilled in the art would understand the terms "esters", "ethers", "acetals", "ketals", and "thiol" as used in the specification. For example, a person skilled in the art would readily comprehend that an ether (R-O-R) becomes an ether substituent when one of the "R" groups is an atom of the chemical group to which the ether is a substituent (e.g., one of the "R" groups is a carbon atom of a heterocyclic ring). Further, the term "esters" is defined at page 3, line 8 with respect to possible C2 substituents to be "R_{2a}C(O)O-". Thus, the connection of this functional group to another atom is clearly defined. Based on this definition, along with the skill of those in the art, the location of the bond connecting the other functional groups can reasonably be inferred by a skilled artisan. Specifically, an "ether" group can be defined as "RO-"; an acetal can be defined as RCH(OR')O- and a "ketal" can be defined as "RC(OR')(OR'')O-". A thiol is generally considered to be the sulfur analog of a hydroxy group. Thus, a thiol group may be represented as -SH.

CONCLUSION

In light of the foregoing, applicants request entry of the claims, withdrawal of all claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issue remain unresolved.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

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*Enclosure

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